REMARKS/ARGUMENTS

The non-final Office Action mailed June 10, 2009 has been carefully reviewed and these remarks are responsive to that Office Action. Claims 1-11, 16-18, and 20-26 were rejected, and claims 12-15, and 19 were withdrawn from further consideration as being drawn to a nonelected invention. As noted in the Office Action, Applicant timely traversed the restriction (election) requirement in the reply filed May 30, 2006. To facilitate prosecution, claim 1 has amended to clarify the invention.

Claim Objections

Claim 1 was objected to because of the following informalities: the phrase, "the composition essentially free of extract from *Emblica Officinalis"* in line 13 is missing an article and a verb. The phrase in claim 1 has been amended in accordance with the Examiner's request to read as "wherein the composition is essentially free of an extract from Emblica officinalis."

Claim Rejections – 35 USC 112 (2nd paragraphs)

Claims 1-11, 16-18 and 20-26 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Office Action rejected claims 1-11, 16-18 and 20-26 under 35 USC-112, second paragraph, as being indefinite based on the phrase "the saponins present in the extract calculated as hederagenin". The Office Action stated that it is unclear whether the applicant is claiming the amount of saponins present is calculated in relation to the amount of hederagenin or that the amount of saponins present contains the claimed percentage of hederagenin.

Claims 1 and 2 of the present invention disclose an anticonvulsant pharmaceutical composition for nasal administration comprising an aqueous, alcoholic, or hydroalcoholic extract comprising a mixture of saponins derived from S*apindus trifoliatus*, the saponins present in the extract **calculated as** hederagenin from 0.004% to 0.08 % w/v with respect to claim 2. It is not

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hederagenin per se which is claimed; rather, it is the amount of saponin which is expressed as hederagenin. Claim 1 claims

"an aqueous, alcoholic, or hydroalcoholic extract comprising a mixture of saponins derived from *Sapindus (S.)trifoliatus*, the saponins present in the extract calculated as hederagenin from 0.001 to 1.0 % w/v." Claim 2 claims "an anticonvulsant pharmaceutical composition, for nasal administration according to claim 1, the saponins present in the extract calculated as hederagenin in an amount from 0.004% to 0.08 % w/v."

As claimed, it is a mixture of saponins that is an aqueous, alcoholic or hydroalcoholic extract comprising a mixture of saponins derived from *Sapindus trifoliatus.* The saponins present in the extract are expressed as hederagenin and are "from 0.001 to 1.0 % w/v" in accordance with claim 1, and "from 0.004% to 0.08 % w/v" in accordance with claim 2. Saponins are a class of secondary metabolites (glycosides of steroids, steroidal alkaloids or triterpenes) widely found in the plant kingdom. In cases of triterpenoid saponins the glycoside units are linked to the triterpene moiety (known as *aglycone*) at its C-3 position (*Trease and Evans' Pharmacognosy,* Fourteenth edn., *1996,* Page 293) (copy with relevant portion concurrently submitted herewith as Annexure 1). The aglycone (i.e., the glycoside-free portion) present in saponins is also termed as sapogenins. The number of saccharide chains attached to the sapogenins/aglycone core may vary giving rise to another dimension of nomenclature (monodesmosidic, bidesmosidic etc).

However, on hydrolysis of saponins, free aglycone is obtained. By measuring the concentration of the aglycone moiety one can arrive at a particular concentration of the total saponins present in an extract. In a few occasions the aglycone part of the saponin is hederagenin. Therefore the Applicant would like to emphasize here that hederagenin is a natural product known in the art and the present invention is not directed to the same *per se*. In the present invention, saponins in the aqueous extract as well as in the formulation, **are related to the amount of hederagenin released during the acid mediated hydrolysis**. The studies of the Applicant have shown that there is no unbound hederagenin in the claimed extracts, as evident from the HPLC and TLC analysis carried out in the laboratory as evident from the HPLC and

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TLC analysis carried out in the laboratory. *See* page 16, line 6 through page 17, line 13 of the present application as originally filed (corresponding to paragraphs [0102] through [0110] of the application as published (Publication No. 2005/0249831)). This disclosure clearly explains the amount of saponins present as expressed as hederagenin. To reiterate the invention, fruit pericarp of the plant *Sapindus trifoliatus* is extracted in water or alcohol or in a mixture of water and alcohol. What is obtained is a specific range of concentration of a mixture of triterpenoid saponins in the extract. The aglycone part in all saponins is hederagenin (compounds 5-10, pages 16-17 of the application as originally filed, and corresponding page 6, paragraphs [0104] through [0109] of the published specification US Publication No. 2005/249831).

Furthermore, it is emphasized that the extract obtained in the present invention possesses anticonvulsant activity. It is important for any therapeutic activity to deliver a known quantity of the active substance. In this case by knowing the quantity of sugars and aglycone, since the ratio is the same (which always happens), the concentration can be measured through the hederagenin obtained by the acid hydrolysis of the saponins. Hence, the saponin quantity in the extract is measured by estimating the hederagenin content (*see* page 7, lines 7-13 of the application as originally filed, and corresponding page 6, paragraph [0110] of the published specification US Publication No. 2005/249831). This is further evident from Row No. 2 of Table –III on page 27 of the application as originally filed, and corresponding page 9, Table III of the published specification US Publication No. 2005/249831, wherein the active ingredient saponin strength is expressed in terms of % w/v hederagenin content.

It has been observed that, in a preferred embodiment, the extract obtained by following the process of the present invention typically contains a mixture of triterpenoid saponins that, when expressed in terms of hederagenin, resides in the range of 0.004 to 0.08 % w/v of hederagenin. The pharmaceutical composition of the present invention derived from the same extract typically contains such saponins that, when expressed in terms of hederagenin in a similar manner, resides in the range of 0.001-1% w/v of hederagenin.

Various batches of the extract of *Sapindus trifoliatus* and composition of the present invention were tested for the triterpenoid saponin content. The results confirm that saponin

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content of the extract remains in the range of 0.004 to 0.08 % w/v of hederagenin, and that of the compositions reside in the range of 0.001-1% w/v.

Thus measurement of hederagenin is an indirect estimation of the triterpenoid saponins present in the extract. The method of estimation has been discussed in depth at the pages 6-9 of the *Declaration of Dr. S. K. Arora* submitted to USPTO on February 9, 2007.

In view of the foregoing, it is respectfully submitted that the pending claims are not indefinite and that they particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Thus, the rejection under 35 USC 112, second paragraph, should be withdrawn.

Claim Rejection – 35 USC 103

Claims 1-5, 16-18 and 20-26 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kiso et al. (JP 06-345650), in view of Gedeon. Claims 1-11, 16-18 and 20-26 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kiso, view of Gedeon, Stern (WO 0156594) and Kagatani et al. These prior art rejections are respectfully traversed.

The present invention discloses an anticonvulsant pharmaceutical composition for nasal administration comprising an aqueous, alcoholic, or hydroalcoholic extract comprising a mixture of saponins derived from *Sapindus trifoliatus*, the saponins presence in the extract calculated as hederagenin from 0.001 to 1.0 % w/v, and at least one pharmaceutically acceptable additive wherein the composition is essentially free of extract from *Emblica offincinalis*.

The invention resides neither in the saponin nor in the hederagenin but the invention resides in a composition which is anticonvulsant and is comprised of extract from *Sapindus trifoliatus* wherein the saponin from the extract are expressed in terms of hederagenin of 0.001 to 1% wt/vol. This does not mean that the amount of hederagenin present is said 0.001 to 1% wt./vol. The inventors have found that the saponins from extract of *Sapindus trifoliatus* is capable of acting as an anticonvulsant and binds with specific binding site and is effective in treatment of migraine.

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Where there are no persuasive reasons to start with a lead compound and then modify that lead compound to form the claimed drug, the claimed drug will be held to be nonobvious. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. June 28, 2007); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358 (Fed. Cir. Mar. 31, 2008); *Eisai Co., Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353 (Fed. Cir. July 21, 2008); *Proctor & Gamble v. Teva Pharm.*, 566 F.3d 989 (Fed. Cir. May 13, 2009).

Here, there is no motivation in the prior art to make an aqueous, alcoholic, or hydroalcoholic extract comprising a mixture of saponins derived from *Sapindus (S.)trifoliatus*, the saponins present in the extract calculated as hederagenin from 0.001 to 1.0 % w/v, and at least one pharmaceutically acceptable additive, wherein the composition is essentially free of an extract from *Emblica officinalis*.

Further, in accordance with *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (Apr. 30, 2007), articulated reasoning with rational underpinning to support the legal conclusion of obviousness is not a matter of listing prior art references and concluding with a stock phrase, "to one skilled in the art it would have been obvious to [obtain the claimed invention]"—the kind of motivation required by the patent laws is not a generalized motivation to develop [the claimed invention], but rather the motivation to combine particular references to reach the claimed [invention]. *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363 (Fed. Cir. Jan. 17, 2008). It is respectfully submitted that the prior art does not provide a motivation to combine particular reference to reach the claimed invention.

The prior art cited document Kiso (JP 06-345650) discloses a composition of treating osteoporosis comprising of hederagenin and is extracted from *Sapindus mukurossi*. The document discloses that the hederagenin can also be used combining various hederagenin compounds as an active principle, although it may be used independently. Kiso further teaches that the composition can be administered intranasally. Further, the carrier for drugs may be added and that the amount of hederagenin is 0.01 to 1% of the weight. Further the composition comprises citrate, potassium chloride, magnesium sulfate, sodium tartarate, and succinic acid.

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As recognized in the Office Action, Kiso does not teach a composition can be used as an anticonvulsant. Kiso does not teach a composition comprising:

i. an aqueous, alcoholic, or hydroalcoholic extract comprising a mixture of saponins derived from *Sapindus (S.)trifoliatus*, the saponins present in the extract calculated as hederagenin from 0.001 to 1.0 % w/v, and

ii. at least one pharmaceutically acceptable additive,

wherein the composition is essentially free of an extract from *Emblica officinalis*.

Gedeon does not remedy the deficiencies of Kiso. Gedeon discloses saponins from Indian soapnut and includes *Sapindus mukorossi* and *Sapindus laurifolius*. Gedeon only teaches extraction of saponin from the out of shells of the nut and that the same has good frothing properties. It also teaches purification of saponins.

The Office Action states that Kiso teaches hederagenin which may be provided intransally and also in amount which is similar to that of the present invention, while Gedeon teaches generally saponin from soapnuts including *Sapindus laurifolius* which is same as *Sapindus trifoliatus*. Accordingly, the Office Action states that saponin from *Sapindus trifoliatus* was known and that saponins contain hederagenin was also known. The Office Action states that the Applicant has only found a new use of known substance and that the use cannot provide inventive feature for the same composition since it would have been inherently present in the Sapindus from the extract.

It is respectfully submitted that what is applicable to *Sapindus mukurossi* cannot be applicable to *Sapindus trifoliatus*. Moreover, the present composition cannot be regarded as merely a new use since the composition of Kiso is for treatment of osteoporosis, which is far away from the treatment of migraine and has totally different route and cause of action. Applicant specifically notes that in accordance with MPEP 2143.01, "Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78

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USPQ2d 1329, 1335 (Fed. Cir. 2006) (discussing rationale underlying the motivation-suggestion-teaching as a guard against using hindsight in an obviousness analysis."

In the present case there is no suggestion or motivation in the prior art to modify Kiso, which is directed to treating osteoporosis, or combine it with other prior art to achieve the claimed composition, which is an anticonvulsant. How a person ordinary skilled in the art would comprehend that saponin in amount expressed as hederagenin as in present invention would act as anticonvulsant for treatment of migraine from teachings of Kiso is not clear from the Office Action. There is no teaching, suggestion or motivation in Kiso to modify or combine it with Gedeon to establish a case of obviousness. In this regard, it is further noted that in accordance with MPEP 2143.01, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, ___, 82 USPQ2d 1385, 1396 (2007)("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

In the present case, there is no teaching in the prior art that the saponin from *Sapindus trifoliatus* can be used in an amount as taught in present claim 1 for a totally new anticonvulsant composition. A composition from saponins of Sapindus mukurossi for treatment of osteoporosis cannot predict a composition from *Sapindus trifoliatus* for treatment of migraine. Moreover, the claimed composition itself is different, as mentioned above, since it is not hederagenin per se whose amount is claimed in claim 1 but saponin being calculated in terms of hederagenin. Again, it is emphasized that the saponin is present in amount, which is calculated as hederagenin, and this cannot be equivalent to hederagenin per se of 0.001 to 1% wt/vol.

There is not slightest hint in the cited documents to modify their disclosures in manner that would result in a product useful towards treating convulsion. Therefore, in the absence of any foreseeable benefit, the cited documents do not provide a reason to a person skilled in the art to modify or combine the prior art to arrive at the invention claimed in the present application.

It is further noted that in accordance with MPEP 2143.01:

VI.THE PROPOSED MODIFICATION CANNOT CHANGE THE PRINCIPLE OF OPERATION OF A REFERENCE

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> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.).

It is evident from above that if a change in basic principles of the prior art is made the same cannot render the invention obvious. In the present situation the composition is from a different species of Sapindus and the same is for a totally different purpose, i.e. an anti-convulsant composition with properties for treatment of migraine, in contrast to composition of osteoporosis as taught in Kiso. *Sapindus trifoliatus* and *Sapindus mukorossi* are two different plant species and it is an established fact that two different plant species can never have same chemical composition (*Critical Reviews in Food Science and Nutrition,* 47 (2007), 231-258: see page 233 explaining saponin content of plant materials is affected by the plant species, a copy of which is concurrently filed herewith as Annexure 2).

Saponins can have same aglycone and the same sugars but with a different sequence and linkages (*J. Chromat. A*, 967 (2002), 147-162 : see page 148 explaining diversity in saponins) (courtesy copy concurrently filed herewith as Annexure 3). A small variation in functional group (such as –OH, -COOH, -CH3) in the aglycone moiety together with a variation in number, chain size, branching pattern, glycosidic attachment and alpha/beta anomerity of the glycone moiety can provide a large array of diverse structures having varying biological properties. The diversity can be further multiplied by regio selective dramatization such as acetylation of a hydroxyl groups present in the sugar moiety.

The intended use of claimed composition of the present invention is for anticonvulsant activity, whereas *Kiso* teaches a composition for treating osteoporosis. The hederagenin compounds in *Kiso* were prepared from the roots of the plant Kalopanax, which is a tree

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belonging to a different family *Araliaceae*, available in northeastern Asia. The compounds mentioned in the Table 1 of *Kiso* are α - hederin, Hed – 3 – ara, Hederagenin and Oeanolic acid (*see* the translated text of JP 6345650 attached herewith). Hence, *Kiso* does not share any compound which the extract of the present invention comprises, as evident from the page 6, paragraphs 0104-0109 of the published specification US Publication No. 2005/249831.

On the other hand, although Gedeon teaches the isolation of crude saponins mixture (and its hydrolysis to hedragenin) from *Sapindus mukorossi* and *Sapindus laurifolius*, it does not provide structural as well as biological activity of the saponins present.

In both Kiso and Gedeon, crude saponin mixtures resulted in the isolation of hederagenin after acid hydrolysis. But, isolation of hederagenin after hydrolysis from both species does not guarantee the presence of same chemical constituents originally present. There are several other reported plant families, which contain diverse saponins having hederagenin as aglycone linkages (*J. Chromat. A*, 1112 (2006), 218-223 : see page 218 (copy attached as Annexure 4) explaining differentiation between two species).

It is noted that the biological activity, namely "anticonvulsant property", claimed in the present invention is not for hederagenin, but for the aqueous extract that contains a mixture of saponins. *See* TLC and HPLC data concurrently attached hereto as Annexures 5 and 6, respectively.

The Office Action rejected claims 1-11, 16-18 and 20-26 under 35 U.S.C. 103(a) as being unpatentable over Kiso et al. (JP 06-345650 A, published December 20, 1994), in view of Gedeon ,in view of Stern (WO 0156594 A1 also published as US 6,440,392 B1),and Kagatani et al. (US Patent No. 4,690,952).

Stern teaches a liquid pharmaceutical composition comprising calcitonin or an acid addition salt thereof and citric acid or salt thereof in a concentration from about to about 50 mM, said composition being in a form suitable for nasal administration. Stern is directed to the making of calcitonin compositions easily bioavailable by application by nasal route. Stern has nothing to do with migraine or anti-convulsant compositions and or a use of saponins.

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Kagatani discloses pharmaceutical compositions for intranasal administration comprising (a) calcitonin and (b) at least one absorption enhancer selected from the group consisting of benzyl alcohol, ethanol, thiamine or a salt thereof, salicylic acid or a salt thereof, capric acid or a salt thereof, Macrogol 400, pyridoxal or a salt thereof, malic acid or a salt thereof and pyrophosphoric acid or a salt thereof, in (c) a liquid diluent or carrier, suitable for application to the nasal mucosa.

Stern and Kagatani do not teach about the use of the composition as an anticonvulsant pharmaceutical. Both Stern and Kagatani are directed to the use of calcitonin, and an effect on bones and treatment for osteoporosis. The Office Action erroneously indicates that the combination of Kiso, Gedeon, Stern, and Kagatani would teach one of ordinary skill in the art at the time of the present invention, without the benefit of the disclosure of the present application, to use saponin from *Sapindus trifoliatus* for the same purpose as in the present invention. It is noted that the present invention does not involve treatment of osteoporosis, but rather treatment of migraine, which is neuro vascular disease and has nothing to do with bones and effect of calcitonin. If saponin for osteoporosis from a certain plant species could motivate development of composition from saponin from another plant species of the same genus for anti-convulsant formulation for treatment of migraine, then any chemical compound for a particular treatment would render a similar compound for different treatment obvious. The purpose is an important feature and it needs to be seen whether a substantially similar substance is being used in substantially same manner to obtain substantial same result. In the present situation neither substantially the substance used is in substantially the same manner nor is the substantially same result achieved. Accordingly this cannot render present invention obvious.

Further, it is submitted that *S. trifoliatus* having this particular amount of hederagenin is capable of producing/ produces effects which is not derivable from the prior art. This may be in terms of ED 50 values, dosage forms, etc., better activity in terms of prophylactic treatment of migraine by reducing the frequency of attack.

Further, Stern and Kagatani do not provide any clue about an extract comprising saponins from *Sapindus trifoliatus* having anti-convulsive property. These documents only provide

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compositions comprising calcitonin and its salts suitable for nasal administration, presumably to treat osteoporosis and related diseases. Drug delivery through nasal route to treat human being is an age-old concept. But apparently there is no nexus between these two documents and the present invention.

Furthermore, in accordance with MPEP sec. 2141.02 (Differences Between Prior Art and Claimed Invention), "**a claimed invention must be considered as a whole**, even if there is a structural similarity between the claimed compound and the compound disclosed by the prior art." *Accord, In re Papesch,* 315 F.2d 381, 137 USPQ 43 (CCPA 1963). In *Papesch*, claims directed to a very close, structurally similar homolog had been rejected by the examiner over a single prior art document. The appellate court held, however, that the claimed compound was nonobvious on the merit of its advantageous pharmacological (anti-inflammatory) property shown not to be possessed by the prior art compound. The court found the case "a single clean-cut issue of law." It has been also established that "the section 103 requirement of unobviouness is no different in chemical cases than with respect to other categories of patentable invention," and the law should be uniformly applicable to any field of science.

The appellate court in *Papesch* cited the classical laevorotatory and dextrorotatory-Arterenol case of 1955 (*Sterling v. Watson, 135 F. Supp. 173, 108 USPQ 37*): "From the standpoint of patent law, a compound and all its properties are inseparable; they are one and the same thing. The graphic formulae, and the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared.... There is no basis in law for ignoring any property in making such a comparison." The take home message from the above discussion is that, just because the present invention and some of the prior arts utilize plants of the same Sapindaceae family, the former should not be considered as obvious. Rather the claimed product and its biological activities should be taken into consideration as a whole to evaluate whether or not it is obvious over the prior art.

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Arguendo, even if, the extract of the present invention shares some active ingredients with that of the prior art, the former cannot be considered as obvious. This is because there is no disclosure that the prior art extracts exhibit anticonvulsive activity.

Conclusion

All rejections having been addressed, applicants respectfully submit that this application is in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,

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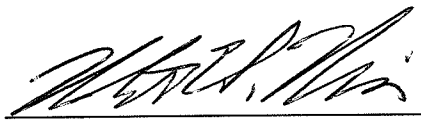
Dated: December 1, 2009

By: 

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